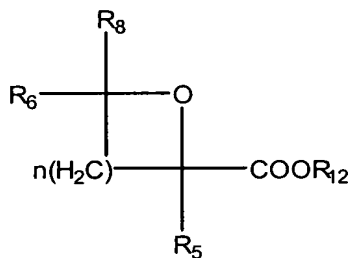


wherein n is included between 0 and 8, R_5 , R_6 , and R_8 are independently hydrogen, a substituted or unsubstituted hydrocarbon radical, the hydrocarbon radical being saturated or unsaturated, linear, branched, or cyclic, $-CH_2COOH$, $-CH_2CO_2Me$, $-CH_3$, $-OH$, OMe , $-CH_2CH_3$, with the proviso that R_5 , R_6 , and R_8 are not hydrogen simultaneously.

The present invention is also directed to cycloalkane esters of the following formula:



wherein n is included between 1 and 8, R_5 , R_6 , and R_8 are independently hydrogen, a substituted or unsubstituted hydrocarbon radical, the hydrocarbon radical being saturated or unsaturated, linear, branched, or cyclic, with the proviso that R_5 , R_6 , and R_8 are not hydrogen simultaneously, and R_{12} is a substituted or unsubstituted hydrocarbon radical, the hydrocarbon radical being saturated or unsaturated, linear, branched, or cyclic, a protecting group of acids or a chiral group with the proviso that R_{12} is not CTX.

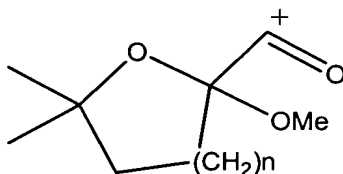
The cycloalkane carboxylic acids and esters, as presently claimed, are novel intermediates in a novel stereoselective synthesis of cephalotaxine derivatives. The cycloalkane carboxylic acids and esters as presently claimed can be used to directly esterify cephalotaxine with preformed stereochemistry.

Claim Rejections under 35 U.S.C. § 103 (a)

Claims 88-101 are rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Wang et al., Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 178-184, 1992 (Wang I) and Huang et al., the Alkaloids, Vol. XXII 157-225, 1984 (Huang) in view of Wang et al., Yaoxue Xuebao (Acta Pharm. Sinica) 27, 173-177, 1992 (Wang II). Applicants respectfully disagree with the rejection; therefore, this rejection is respectfully traversed.

English translations of Wang I and Wang II have been obtained and are enclosed herewith for the Examiner's convenience.

Wang I discloses a tetrahydrofuran and tetrahydropyran ester of cephalotaxine. The synthesis and the starting materials used to obtain these esters is disclosed in Wang II. It is respectfully submitted that neither Wang I nor Wang II teach or suggest syntheses using cycloalkane carboxylic acids or cycloalkane esters, as presently claimed. Wang II teaches the synthesis of the tetrahydrofuran and tetrahydropyran esters of cephalotaxine of Wang I by esterification using mixed cyclic acetals, such as the following intermediate:

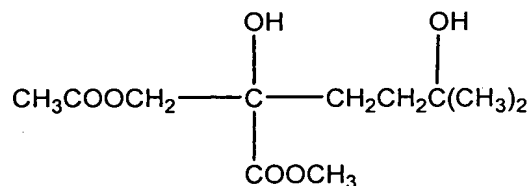


After esterification using the mixed cyclic acetals, Wang II teaches a subsequent alpha-hydroxyalkylation using methyl bromoacetate and active zinc under conditions of the Reformatsky reaction to provide a linear ester. The linear ester may then be re-cyclized using p-toluene sulphonic acid to provide a tetrahydrofuran and tetrahydropyran ester of cephalotaxine, as disclosed in Wang I (compounds 8 and 9).

Since Wang I and Wang II teach synthesis of cephalotaxine derivatives using mixed cyclic acetals followed by a Reformansky reaction and subsequent cyclization, neither Wang I nor Wang II teach or suggest syntheses using cycloalkane carboxylic acids or cycloalkane esters, as presently claimed. Therefore, neither Wang I nor Wang II teach or suggest the cycloalkane carboxylic acid and ester intermediates as presently claimed.

As part of a structural study of cephalotaxine alkaloids, Huang teaches mild transesterification of the "harringtonines" to yield cephalotaxine and the respective dimethyl

esters of hydroxydicarboxylic acids (compounds 7-10). All of these hydroxydicarboxylic acids are linear nor cyclic compounds. For example compound 7 is as follows:



Huang teaches methods to determine which of the carboxyl groups of the dimethyl esters of hydroxydicarboxylic acids was originally esterified in cephalotaxine. Huang relates to determining the gross structures of the harringtonines. Therefore, Huang is concerned with determining the structures of the four closely related dimethyl esters of the harringtonines. As described above, Wang II relates to synthesizing cephalotaxine derivatives.

There is no teaching or suggestion in Wang II or Huang to combine the methods of synthesis and resulting cephalotaxine derivatives of Wang II with the methods to determine which of the carboxyl groups of the dimethyl esters of hydroxydicarboxylic acids was originally esterified in cephalotaxine of Huang. Neither Wang II nor Huang teach or suggest the cycloalkane carboxylic acid and ester intermediates as presently claimed.

Conclusion

For the reasons noted above, the art of record does not disclose or suggest the inventive concept of the present invention as defined by the claims.

In view of the foregoing remarks, reconsideration of the claims and allowance of the subject application is earnestly solicited. The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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